selected triphosphate to add a homopolymeric sequence to the 3'-end. The Examiner concludes, therefore, that the '064 application establishes a "nexus" between the use of TdT and triphosphate nucleoside compounds in the synthesis of polynucleotide compounds, thus rendering the claimed methods and compositions obvious.

Applicants respectfully traverse the rejection because the teachings of the cited references do not teach or suggest the claimed invention. The claimed invention is directed to a method for synthesizing a polynucleotide of a predetermined sequence. Specifically, the method entails the use of a template-independent enzyme to form a 5' to 3' phosphodiester linkage between an unprotected 3' hydroxyl group of an initiating substrate with the 5'-phosphate of a nucleoside 5'-triphosphate having a removable blocking moiety protecting the 3' position of the 5'-triphosphate. *Hyman* mentions the use of RNA ligase to enzymatically synthesize oligonucleotides; however, in the *Hyman* process, RNA ligase catalyzes the coupling of 5'-monophosphates to 3'-hydroxyls -- the RNA ligase is inactive towards 5'-triphosphates with respect to forming phosphodiester bonds. Thus, triphosphates simply cannot be added to nucleotide chains under the conditions disclosed by *Hyman*. There is no disclosure of an enzyme that is capable of forming a phosphodiester bond formation via a 5'-triphosphate group. Thus, the teachings *Hyman* do not render obvious Applicants' invention.

The Examiner's reference to Figure 1 of *Hyman* does not support the conclusion of obviousness. Figure 1 summarizes two prior art approaches to the enzymatic synthesis of oligonucleotides, namely the "uncontrolled" method and the "blocked" method. According to *Hyman*, the "uncontrolled" method utilizes a short oligonucleotides primer, which is incubated with a desired nucleotide and a nucleotidyl transferase (e.g., TdT). See col. 1, lines 21-53. *Hyman's* opinion is that this method is "flawed" because at the end of the incubation period, a mixture of oligonucleotides products of different lengths is obtained. This result is in sharp contrast to Applicants' claimed invention in which a single nucleotide is added. *Hyman* describes the "blocked" approach as utilizing a nucleotide that is blocked in some manner to prevent the enzyme from adding additional nucleotides to the oligonucleotide primer. After the extension step, the oligonucleotide product is separated from the enzyme and nucleotide, and the blocking group is removed. Examples of this method include the use of polynucleotide phosphorylase ("PNP") with NDP-2'-acetal blocked nucleotides to make oligoribonucleotides, and RNA ligase with the blocked nucleotide App(d)Np (or ATP + 3', 5'-(d)NDP) to make oligoribonucleotides and oligodeoxyribonucleotides. See col. 1,

line 54 to col. 2, line 7. Hyman describes this method as flawed, too. The use of TdT and 5'-triphosphates is neither taught nor suggested in this approach.

The Examiner also believes that *Hyman* teaches the "interchangableness" of TdT and RNA ligase. Applicants disagree. *Hyman* merely teaches that unreacted primer chains may be capped with a chain terminating nucleotide using a combination of TdT and a dideoxynucleoside triphosphate (ddNTP), or RNA ligase and AppddN (a dideoxy analog of AppddN). There is no teaching or suggestion that TdT can be used in place of RNA ligase for the directed synthesis for oligonucleotides. Moreover, *Hyman* does not teach or suggest that the ddNTP cap added by TdT may be removed for the further directed synthesis of oligonucleotides, but just that the capped oligonucleotides may then be selectively hydrolyzed using an exonuclease. *Hyman* therefore fails to teach or suggest the nucleotide triphosphate-based method of the present invention. Reconsideration and withdrawal of the rejection based on the *Hyman* reference are therefore respectfully requested.

Applicants also traverse the rejection based on the '064 application. The '064 application is simply directed to homopolymeric tailing of an oligonucleotide. There is no teaching or suggestion of directed synthesis of oligonucleotides using a template-independent enzyme such as TdT. The '064 application teaches a method of selectively amplifying nucleic acid fragments having a known sequence. Sense-strand fragments containing a known sequence are primed with a sequence-specific primer having a sequence that is homologous to the known sequence. The sequence is subsequently replicated in the presence of the template-dependent enzyme, DNA polymerase to form anti-sense strands having the proper sequence at their 5'-ends. The anti-sense strands are then treated with TdT and a selected deoxynucleoside triphosphate to add a homopolymeric sequence (tail) to the 3'-strand ends. The resulting anti-sense strand fragments are mixed with a homopolymer primer which is homologous to the homopolymeric fragment sequence, a common-sequence primer that is homologous to a region of the specific-sequence primer, DNA polymerase and all four deoxynucleoside triphosphates. The newly synthesized fragments are subsequently amplified by repeated cycles of primerannealing, polymerization and denaturation. See page 3, line 25 through page 4, line 10. The tailing reaction utilizing TdT simply adds a series of unblocked nucleotides to the end of the anti-sense strand, similar to the method described and illustrated in the *Hyman* patent. Plainly, there is no teaching or

suggestion of directed synthesis of oligonucleotides using a template-independent enzyme such as TdT, as claimed by Applicants.

In view of the foregoing, reconsideration and withdrawal of the rejection are requested.

Applicants submit that the present remarks serve to overcome the outstanding rejections and place the claims in condition for allowance. An early Notice to this effect is therefore solicited. The Examiner is invited to contact the undersigned if he has any questions.

Finally, if there are any additional charges in connection with this response, the Examiner is authorized to charge Applicants' Deposit Account No. 12-1095 therefor.

Respectfully submitted,

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